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3/25/03

Office Action Summary

Application No. 10/091,500	Applicant(s) AMINO ET AL.	
Examiner Paul A. Zucker	Art Unit 1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 January 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-15, 17-24 and 26-39 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-15, 17-24 and 26-39 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>9</u> . | 6) <input type="checkbox"/> Other: |

DETAILED ACTION

Current Status

1. This action is responsive to Applicants' amendment of 9 January 2003 in Paper No 8.
2. Receipt and entry of Applicants' amendment is acknowledged.
3. Applicant's cancellation of claims 16 and 25 is acknowledged.
4. Claims 1-15, 17-24, and 26-39 are pending.
5. The objections to the specification set forth in paragraphs 2a and 2b of the previous Office Action in Paper No 6 are withdrawn in response to Applicant's amendment.
6. The objection to the claims set forth in paragraph 3 of the previous Office Action in Paper No 6 is withdrawn in response to Applicant's cancellation of claim 25.
7. The rejections under 35 USC § 112, second paragraph, set forth in paragraphs 4 - 16 of the previous Office Action in Paper No 6 are withdrawn in response to Applicants' amendment and remarks.
8. The rejections under 35 USC § 112, first paragraph, set forth in paragraph 17 of the previous Office Action in Paper No 6 is withdrawn in response to Applicants' remarks.
9. The rejection under 35 USC § 102(b) set forth in paragraph 18 of the previous Office Action in Paper No 6 is withdrawn in response to Applicants' amendment.
10. Applicants argue (Amendment, page 13, first line) in response to no particular rejection that the cited references contain no disclosure of "such a granulated sweetener" and therefore cannot affect the patentability of the present claims. The

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Examiner agrees that a "granulated sweetener" is not disclosed by the references but disagrees and points out that the limitation "granulated sweetener" is not required by the instant claims.

11. Claims 23, 24 and 26 are finally rejected under 35 U.S.C. 102(b) as being anticipated by Nofre et al (US 5,480,668 01-1996). Nofre discloses (Column 8, Table 1, entries 18 and 19 and column 7, lines 24-51) the compounds N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester and its corresponding unsaturated counterpart and their crystallization from alcohol solvent. Compounds are distinguished by their atoms and bonds and not by their method of production. The diffraction peaks are an inherent property of the compound disclosed by Nofre. Claims 23, 24 and 26 are therefore anticipated by Nofre et al.

Examiner's Response to Applicants' Remarks With Regard to This Rejection

12. Applicant argues that Nofre does not describe that the series can be purified with the same or similar solvents. The Examiner points out that Applicants' are attempting to claim the product resulting from the crystallization process. Applicants' have not distinguished the compound disclosed by Nofre from that instantly claimed. The properties of the compound disclosed by Nofre, including crystallinity and diffraction pattern, are considered by the Examiner to be inherent properties of the compound disclosed by Nofre.

Applicant's arguments filed 9 January 2003 have been fully considered but are not persuasive for the reasons indicated above.

13. Claims 27 and 28 are finally rejected under 35 U.S.C. 102(b) as being anticipated by Nofre et al (US 5,480,668 01-1996). Nofre discloses (Column 10, lines 42-47, claims 6 and 7) the use of the instantly claimed compound of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester as a sweetening agent in combination with carriers or bulking agents. Claims 27 and 28 are therefore anticipated by Nofre.

Examiner's Response to Applicants' Remarks With Regard to This Rejection

14. Applicants argue that at least for the same reason indicated for the previous rejection claims 27 and 28 are patentable over Nofre. The properties of the compound disclosed by Nofre, including crystallinity and diffraction pattern, as discussed above, are considered by the Examiner to be inherent properties of the compound disclosed by Nofre. Nofre's use of this compound is therefore also considered to be anticipatory of instant claims 27 and 28.

Applicants' arguments filed 9 January 2003 have been fully considered but are not persuasive for the reasons indicated above.

15. Claims 1- 6, 8, 9, 13-15, 17-22, 30 -32, 34, 35, 38 and 39 are finally rejected under 35 U.S.C. 103(a) as being unpatentable over Nofre et al (US 5,480,668 01-1996) in view of Claude et al (US 5,510,508 04-1996).

Nofre teaches (Column 8, Table 1, entries 18 and 19) the compounds N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester and its unsaturated counterpart. Nofre further teaches (Column 7, lines 24-51) a general

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process for its synthesis. Nofre teaches a process for reductive alkylation of aspartame with the appropriate aldehyde (1.099 molar ratio aldehyde/aspartame) in methanol at room temperature for 24 hours. Nofre teaches removal of the reaction solvent (methanol) washing with aqueous HCl (to remove aspartame) and its replacement with ethanol/water as a recrystallization solvent (solvent substitution). Aspartame as well as other impurities, is removed via the disclosed crystallization.

Instantly claimed is a method for the production of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester comprising subjecting 3-(3-methoxy-4-hydroxyphenyl) propionaldehyde and Aspartame to reductive alkylation via hydrogenation in the presence of a catalyst followed by crystallization.

The difference between the process taught by Nofre and the instant process is that Nofre teaches a process for reductive alkylation which employs sodium cyanoborohydride as a reductant while the instant application claims the use of a catalytic hydrogenation reaction. Additional differences are that Nofre does not indicate the pH of the process

Claude, however, teaches (Column 3, line 63- column 4, line 26) a reductive alkylation reaction between 3,3-dimethylbutyraldehyde and aspartame in methanol solution in the presence of platinum catalyst and hydrogen gas at 1 bar at room temperature. Claude teaches (Column 3, lines 8-11) the use of both palladium and

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platinum as catalysts. Claude further teaches (Column 3, lines 45-48) reaction at a pH of 4.5-5.

Thus the instantly claimed process would have been obvious to one of ordinary skill in the art. The suggestion to combine is found in the nearly identical fields of invention. The motivation would have been to modify the general process for the synthesis of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester taught by Nofre by replacing his conditions for reductive alkylation with those taught by Claude. The expectation for success would have been very high based on the fact that one equivalent process was being replaced by another.

Examiner's Response to Applicants' Remarks With Regard to This Rejection

16. Applicants have put forth several arguments with regard to this rejection. The

Examiner responds to these below:

- a. Applicants argue that the combination of catalytic hydrogenation using Pd on carbon with an aldehyde derivative having an aromatic ring is neither disclosed nor suggested in these references. The Examiner disagrees and points out that substitution of the catalytic hydrogenation taught by Claude for the production of neotame into the synthesis of neotame taught by Nofre and extension of the resulting process to synthesis of the analogue N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester produces the instant process.

- b. Applicants further argue that these references would lead one of skill in the art away from the presently claimed methods since Claude discloses that catalytic hydrogenation with hydrogen and other metal catalysts gives rise to secondary reactions to form by-products. The Examiner agrees with Applicants' summary of Claude's teaching but disagrees with Applicants' conclusion therefrom. Claude, in fact, teaches (Column 3, lines 49-57) that the catalyst of the instant invention overcomes the problems resulting from the use of other catalysts. This would direct one toward the instantly claimed process not away as argued by Applicants.
- c. Applicants argue that since Claude only discloses application of the Pd-carbon catalyst to the synthesis of Neotame, Claude therefore suggests that catalytic hydrogenation cannot be applied to the instant case since one would have assumed that an aromatic ring would undergo reduction under hydrogenation conditions. The Examiner disagrees and points out that Applicants' conclusion is not supported by the facts on record. The record supports the opposite conclusion for the following two reasons:
 - i. Aspartame itself contains an aromatic ring in the phenylalanine amino acid side chain which clearly survives under Claude's hydrogenation process. There is no reason why one of ordinary skill in the art would not therefore expect that an aromatic ring located in the aldehyde reactant would not demonstrate similar stability under Claude's conditions.

- ii. Claude teaches (Column 3, lines 8-26) that the use of Pd-carbon obviates the difficulties encountered with hydrogenation of the aromatic ring of Aspartame.

Applicant's arguments filed 9 January 2003 have been fully considered but are not persuasive for the reasons indicated above.

17. Claims 7, 10-12, 33 and 36-37 are finally rejected under 35 U.S.C. 103(a) as being unpatentable over Nofre et al (US 5,480,668 01-1996) and Claude et al (US 5,510,508 04-1996) as applied to claims 1- 6, 8, 9, 13-15, 17-22, 31, 30 -32, 34, 35, 38 and 39 above and further in view of Prakash et al (US 6,077,962 07-2000).

Instantly claimed is a method for the production of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester comprising subjecting 3-(3-methoxy-4-hydroxyphenyl) propionaldehyde and Aspartame to reductive alkylation followed by an extractive workup and crystallization. The use of the same solvent for reductive alkylation and crystallization is claimed as well.

The difference between the process taught by Nofre and Claude and the instant process is that Nofre prefers crystallization without a previous extractive workup.

Prakash, however, teaches (Column 14, line 48- column 15, line 32) a process for the synthesis of N-neohexyl- α -aspartame (neotame). Prakash further teaches extractive workup of the product neotame using water-ethyl acetate followed by

recrystallization from methanol -water. Methanol was used as the solvent for reductive alkylation as taught by Prakash.

Thus the instantly claimed process would have been obvious to one of ordinary skill in the art. The motivation would have been to improve the process taught by Nofre modify using the extractive workup suggested by Prakash. Since the fields of invention are the same (synthesis of aspartame derivatives such as neotame) there would have been a reasonable expectation for success.

Examiner's Response to Applicants' Remarks With Regard to This Rejection

18. Applicants have put forth several arguments with regard to this rejection. The

Examiner responds to these below:

- a. Applicants argue that Prakash is directed toward the synthesis of neotame and is completely unconcerned with N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester. The Examiner agree with this statement but points out that all the other references are also concerned with neotame and this common concern reinforces the propriety of their combination.
- b. Applicants further argue that there is no disclosure of the solubilities of the various compounds in the claimed process. While the Examiner agrees that there is no explicit discussion of the various solubilities, one of ordinary skill in the art would have understood that Neotame and N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester are both Aspartame derivatives which are N-alkylated with bulky hydrophobic

substituents. Given the relationship of the two compounds as analogues, there would have been a reasonable expectation on the part of one of ordinary skill in the art that a process which was successful for Neotame would also be successful for N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester.

Applicant's arguments filed 9 January 2003 have been fully considered but are not persuasive for the reasons indicated above.

19. Claim 29 is finally rejected under 35 U.S.C. 103(a) as being unpatentable over Nofre et al (US 5,480,668 01-1996) and Claude et al (US 5,510,508 04-1996) as applied to claims 1- 6, 8, 9, 13-15, 17-22, 30-32, 34, 35, 38 and 39 above and further in view of Solomons (Organic Chemistry 1992, John Wiley & Sons, Inc. New York, pages 305-311).

Instantly claimed is a method for the production of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester comprising subjecting 3-(3-methoxy-4-hydroxyphenyl) propenylaldehyde and Aspartame to reductive alkylation. The simultaneous reduction of the intermediate imine and the double bond in the starting aldehyde is claimed as well.

The difference between the disclosure of Nofre and Claude and the instantly claimed process is that Nofre does not produce N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester via reduction of the double bond in the

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3-(3-methoxy-4-hydroxyphenyl) propenylaldehyde but instead uses the reduced aldehyde as starting material. Using 3-(3-methoxy-4-hydroxyphenyl) propenylaldehyde as starting material, however, is obvious in the process of Nofre as modified by the teaching of Claude since Nofre teaches both unsaturated and saturated aldehydes as starting materials. One of ordinary skill in the art would recognize that when the reductive alkylation was carried out via catalytic hydrogenation instead of sodium cyanoborohydride treatment the double bond in the unsaturated aldehyde would automatically be reduced to give the saturated product.

Solomons teaches (Page 305) the catalytic hydrogenation of alkenes to give the saturated compounds.

Thus the instantly claimed process would have been obvious to one of ordinary skill in the art. The suggestion for combination of the references would have been found in the recognition of the chemistry involved and the motivation would have been to eliminate a synthetic step resulting in an increase in the cost effectiveness of the process for synthesis of commercial sweeteners.

Examiner's Response to Applicants' Remarks With Regard to This Rejection

20. Applicants have put forth several arguments with regard to this rejection. The Examiner responds to these below:

- a. Applicants argue that the application of hydrogenation reactions to cinammaldehyde is problematic and provides references to support this contention. In particular, Applicants point out that, with palladium catalysts,

decarboxylation, reduction to the corresponding alcohol with subsequent hydrogenolysis of the reduction product all occur. Applicants argue that these reactions all compete with reduction of the imine. The Examiner, however, points out the following:

- i. The conditions under which cinnamaldehydes undergo the above-mentioned competing side reactions are not indicated in Nishimura. Claude, in fact, teaches that mild conditions should be employed to avoid side reactions. It is not at all clear from Nishimura that the above-mentioned side reactions would be expected under the mild conditions of Claude.
 - ii. All of the above-mentioned side reactions depend upon the initial reduction of the aldehyde to the alcohol. Once the aldehyde has been converted to the imine reduction of the aldehyde to the alcohol is impossible and therefore all other side reactions are avoided. The evidence presented does not support Applicants' implied assumption that reduction of the aldehyde of a cinnamaldehyde is faster than formation of the corresponding imine with a primary amine.
- b. Applicants further argue that side reactions occur with Raney Nickel catalyst. The Examiner points out that the hydrogenation reaction of cinnamaldehydes in the presence of Raney Nickel catalyst is irrelevant in this context.

- c. Applicants argue that the same side reactions that occur with palladium occur with platinum catalysts. The Examiner points out that the response to Applicants' arguments regarding palladium catalysts applies here as well.

Applicant's arguments filed 9 January 2003 have been fully considered but are not persuasive for the reasons indicated above.

Conclusion

21. Claims 1-15, 17-24, and 26-39 are pending. Claims 1-15, 17-24, and 26-39 are finally rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul A. Zucker whose telephone number is 703-306-0512. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 703-308-4532. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Paul A. Zucker
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March 21, 2003


Johann Richter, Ph.D., Esq.
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